REMARKS

The final Office action dated February 23, 2004 is acknowledged. Claims 1, 3-9 and 11-18 are pending in the instant application. According to the Office action, each of those claims has been rejected. By the present "Reply to Final Office Action," claims 1, 15 and 18 have been amended. Reconsideration is respectfully requested in light of the amendments being made hereby and of the following remarks.

Rejection of Claims 1, 3-9 and 11-18 under 35 U.S.C. 112, first paragraph

Claims 1, 3-9 and 11-18 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Specifically, the Examiner states that some of these claims contain subject matter (i.e., that the polyacrylate not comprising an amino group) is not disclosed in the specification and so is new matter. The applicants submit that this term has been deleted from the claims. Withdrawal of this rejection is respectfully requested.

The claims were also rejected as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicants regard as the invention. The Examiner states that the claims are confusing regarding the recitation of the supersaturated reservoir because in order to have a supersaturated reservoir, there should be a solvent that dissolves the active agents until it reaches saturation, and then rendered supersaturated by other elements such as heat or adding crystallization inhibitors.

The applicants respectfully submit that the transdermal patches of the present invention do not need to contain typical solvents which are suitable for dissolving steroid

hormones, as the solvents which are used to dissolve the various ingredients are removed by drying (page 4 of the specification, Ex. 1; page 5, last paragraph).

The applicants also submit that it is commonly accepted in the transdermal delivery technology field that active substance compounds such as estrogens are dissolved within the polymeric matrix, which forms the reservoir of most types of transdermal therapeutic systems. For example, Fischer et al. '711 teaches that "pressure-sensitive acrylate adhesives ... have good dissolving properties for oestradiol and norethisterone acetate" (col. 3, lines 58-62). Lehmann et al. '999 also teaches that "acrylic copolymers are formulated as a transdermal therapeutic system in the form of a solution with the drug" (col. 2, lines 6-8). In addition, WO '227 states "oestradiol and NETA are in supersaturated solid solution in the copolymeric matrix" (page 6, last sentence). The term "solid solution" refers to the fact that the active ingredients are "dissolved" within the polymer of the matrix, which is solid. Therefore, for supersaturating the polymer matrix with active substances, the polymer matrix does not need to contain any further solvents, although solvents are used to dissolve or suspend the ingredients, and are later removed, as mentioned above.

The applicants further submit that the supersaturated state of the reservoir can be brought about in multiple ways. First, the active ingredients could be added at a sufficiently high concentration (or even as crystalline substances) so that some excess of these ingredients could not be dissolved in the polymer matrix, but would instead be dispersed as solid particles. Secondly, the matrix could be produced such that the active ingredients would be completely dissolved in the polymer(s) of the matrix. In this case,

supersaturation could occur when the dissolving capacity of the polymer matrix is reduced afterwards, for example, if the matrix becomes hydrated during storage or when the transdermal system is applied to the skin of a person. This phenomenon is described in Fischer et al. '711 (col. 6, lines 27-44) and claim 1 thereof, as well as in the present specification at page 1, second paragraph ("...in the case of supersaturation, unwanted crystallization occurs during storage."). Although supersaturation is "unwanted" during storage, it is beneficial while the transdermal system is applied to the skin since it causes an increase in the thermodynamic activity of the active ingredients (Fischer et al. '711, col. 6, lines 38-44). In all cases, however, supersaturation increases the risk of recrystallization, which must be avoided.

In paragraph 4 of the Office action, the Examiner states that "other elements such as heating or adding crystallization inhibitors" would be required to render the reservoir supersaturated. However, the applicants respectfully submit that these "other elements" are not absolutely required for this purpose. In the process which is used for making the transdermal therapeutic systems of the present invention, heat may optionally be used to accelerate the removal of solvents in which the polymers and other ingredients were initially dissolved or suspended (Example 1, pages 4-5, of the specification). The step of solvent evaporation, however, is common to all solvent-based manufacturing processes for producing transdermal patches and is not a specific requirement when making supersaturated systems. Moreover, the addition of a crystallization inhibitor is not required to obtain a supersaturated system. These inhibitors are added to prevent an unwanted, disadvantageous effect (i.e., crystallization) which occurs in such

supersaturated systems. This is also explained in Fischer et al. '711 at col. 4, lines 7-16. The applicants respectfully submit that it would be incorrect to state that the active substance-containing reservoir is rendered supersaturated by adding a crystallization inhibitor.

The applicants also submit that the composition of supersaturated transdermal systems, and general methods for producing such systems, are well known in the art. In general, "supersaturation" refers to the fact that the active ingredients are present above their saturation concentration, as stated in Fischer et al. '711, col. 3, lines 21-28. Likewise, methods for determining solubility of active substances in a polymeric matrix are known to the person of ordinary skill in the art, as set forth in Fischer et al. '711, col. 5, lines 29-48.

Based on the foregoing, the applicants hope that a sufficient explanation and clarification as to what the Examiner deems confusing in paragraph 4 of the Office action has been provided, especially with respect to the recitation of "supersaturated systems" in the claims. Moreover, in order to further clarify this terminology, the applicants have amended claims 1, 15 and 18. Therefore, it is respectfully requested that this rejection be withdrawn.

Rejection of Claims 1, 3-9 and 11-15 under 35 U.S.C. 103(a)

Claims 1, 3-9 and 11-18 have been rejected as being unpatentable over U.S. Patent No. 5,730,999 (Lehmann et al.) in view of any of U.S. Patent No. 5,683,711 (Fischer et al.) or WO 97/23227 (Cordes et al.). It is respectfully submitted that these claims in their present form are patentably distinct from the prior art.

The Examiner essentially states that it would have been obvious to one having ordinary skill in the art to provide a transdermal drug delivery device comprising a reservoir of acrylate adhesive comprising hormones and a mixture of polymer having no amino group and amino group containing polymer as disclosed by Lehman et al. '999, and to replace the hormones by the supersaturated state of the hormones as disclosed by either Fischer et al. 711 or WO '227. The motivation for doing so, according to the Examiner, is found in Fischer et al. '711 where it states the supersaturation is desirable and necessary in order to impart a high thermodynamic activity to drugs which permeate with difficulty. Additional motivation, according to the Examiner, is found in WO '227 where it teaches that the transdermal patch comprising oestradiol and NETA in supersaturated state in the copolymeric matrix is the condition which confers to the active ingredients activity required for a forced diffusion through the skin even in absence of absorption enhancer, and could release constant amounts of the drugs during its whole possible application time from 3-7 days, with reasonable expectation of having a transdermal delivery device comprising a combination of oestradiol and NETA in a supersaturated state in a mixture of amino-containing polymer and amino-free polymer without crystallization that deliver the combination of the hormones to the patient in need with great success.

The applicants respectfully disagree with this conclusion and submits that independent claims 1, 15 and 18 of the present application contain the limitation in which the crystallization inhibitor is an amino group-containing polymer selected from the group consisting of polyaminoamides, polyaminoimidazolines, polyetherurethaneamines,

polyamines and polyglucosamines. Moreover, the applicants submit that Lehmann et al. '999 fails to teach or disclose an amino group-containing polymer which is included in the aforementioned group of polymeric compounds, and which is added to the reservoir as a crystallization inhibitor. At page 5, lines 1-2 of the Office action, the Examiner states that Lehmann et al. '999 mentions methacrylamide as an example of an amino-containing polymer. However, the methacrylamide compound (Lehmann et al. '999, col. 3, lines 48-51) is a co-monomer which is used to prepare functional poly(meth)acrylates (col. 3, lines 32-41; 47-51; 55-58; and col. 4, lines 1-16). In other words, the methacrylamide is not a polymer by itself, but rather is a co-monomer of a poly(meth)acrylate copolymer containing functional groups. Moreover, an methacrylamide-containing poly(meth)acrylate copolymer is still an acrylate copolymer and would not belong to any one of the substance classes set forth in claims 1, 15 or 18, namely, polyaminoamides, polyaminoimidazolines, polyetherurethaneamines, polyamines and polyglucosamines.

As stated above, the Examiner acknowledged that Lehmann et al. '999 fails to disclose the specific species of the amino-containing polymer. However, the Examiner's opinion is that it would have been within the skill in the art to replace one species by another when both are known to perform the same function. To this end, the applicants respectfully submit that Lehmann et al. '999 teaches amino-containing polymers having a different function than those of the present application. According to the reference, a selected mixture of polyacrylates having cationic, anionic or hydrophilic character is used to control the release of drug to the skin (col. 2, lines 32-43; 47-55; col. 3, lines 14-17). It

is the applicants' position that Lehmann et al. '999 fails to teach or suggest that the amino-containing polyacrylates might have a crystillzation-inhibitory effect. Moreover, the reference does not refer to supersaturated reservoirs, in particular to reservoirs supersaturated with a combination of oestradiol and norethisterone acetate. The applicants submit that the crystallization-inhibiting function of polyaminoamides, polyaminoimidazolines, polyetherurethaneamines, polyamines and polyglucosamines was not even known in the relevant art prior to the present invention. Therefore, the applicants submit that it would not be possible for one skilled in the art to have motivation to replace the amino group-containing methacrylate copolymer of Lehmann et al. '999 with the amino group-containing polymers according to the present invention.

Still referring to Lehmann et al. '999, the examples 4-12 provided therein concern formulations containing ketoprofen which is an acidic compound and is not at all related with the active substances used in the present invention. Examples 1-3 of Lehmann et al. '999 concern formulations containing prednisolone (a cortisone-related steroid). In these examples, a methacrylate copolymer containing acidic co-monomers (i.e. methacrylic acid) is used (Example 2). Therefore, the applicants respectfully submit that it appears Lehmann et al. '999 actually suggests using an acidic polymer, rather than an amino group-containing polymer, in cases where steroids are used as an active substance. Moreover, nowhere in Lehmann et al. '999, not even in the numerous examples, is a formulation containing estrogen or gestagen, or a combination of both, taught or suggested.

Referring now to Fischer et al. '711, the reference teaches to add vitamin E or a vitamin E derivative, such as tocopherols, to inhibit recrystallization in a supersaturated transdermal system containing oestradiol and norethisterone acetate (col. 3, lines 58-62; col. 4, lines 3-33; Examples 1 & 7). The crystallization inhibitors of this reference are not polymers. Moreover, it is respectfully submitted that the do not belong in the group of amino group-containing polymers set forth in the claims of the present application.

WO '227 teaches to use octyl dodecanol as a crystallization-inhibiting substance in a transdermal reservoir supersaturated with oestradiol and norethisterone acetate (page 6, last paragraph – page 7, line 12). The applicants respectfully submit that octyl dodecanol is not an amino group-containing polymer.

In summary, the applicants submit that Lehmann et al. '999 does not teach any crystallization inhibiting substance, and further, does not teach or disclose a substance falling within the group of amino group-containing polymers as set forth in the present claims. Moreover, Lehmann et al. '999 does not refer to supersaturated systems containing a combination of oestradiols and norethisterone acetate. Fischer et al. '711 and WO '227 teach crystallization-inhibiting substances which are not polymers and which do not belong in the group of crystallization inhibitors set forth in present claim 1. Additionally, it is respectfully submitted that both of these references fail to make up for the aforementioned deficiencies of Lehmann et al. '999. To this end, the applicants submit that if one skilled in the art were to have modified the transdermal drug delivery device of Lehmann et al. '999 by replacing the hormones by the supersaturated state of hormones disclosed by either Fischer et al. '711 or WO '227, one would still not have

been able to provide the transdermal system defined in the present claims as there would not no reasonable expectation of success. Specifically, there would be no reasonable expectation that the amino group-containing polymers of the present invention would be effective as crystallization inhibitors of oestradiol and norethisterone under supersaturated conditions. Based on the foregoing arguments and deficiencies of the prior art references, it is respectfully submitted that the obviousness-type rejection be withdrawn.

Conclusion

For the foregoing reasons, it is respectfully submitted that the present application is in condition for allowance, and such action is earnestly solicited. The Examiner is invited to call the undersigned if there are any remaining issues to be discussed which could expedite the prosecution of the present application.

Respectfully submitted,

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